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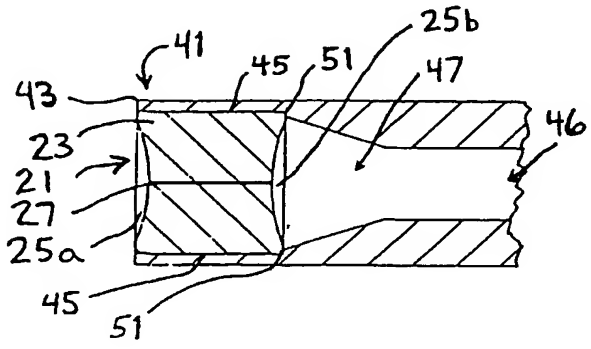

(57) Abstract: A pre-slit septum (21), adapted to be compressed by an access port of a device (41), allows for insertion of a tip into the slit (27) while the slit sealingly engages and closes around an outer surface of the inserted tip, in providing a leak-proof seal that is a barrier to contamination. Preferably, the elastomeric septum further comprises an antimicrobial agent to inhibit microbial growth on septum surfaces (25a & b). Also provided is a septum-access port assembly (41), adapted to sealing engage a tip, comprising an access port adapted to receive and compress the elastomeric septum (21), which is held in position by, and compressed by the access port septum receiving portion (45).

WO 02/066595 A1

ACCESS PORT SEPTUM AND ASSEMBLY

This is an international patent application filed under the Patent Cooperation Treaty in the United States Receiving Office that claims priority to U.S. patent application no. 09/707,588 filed 7 November 2000 and U.S. patent application no. 09/717,651 filed 21 November 2001, the latter of which is a continuation in part of the prior, the disclosures of which are both herein incorporated by reference in their entirety.

Field of the Invention

The present invention relates to a septum for use in access ports of vessels; and more particularly to a self-sealing, compressed septum for providing and maintaining a leak-proof, sterile seal.

Background of the Invention

Typically, access ports permit a user to access fluids; i.e., introduce fluids into a reaction vessel or withdraw fluids contained within the reaction vessel. In biological fluid handling operations, it is further necessary to permit access to the reaction vessel while maintaining a sterile environment inside the reaction vessel. To accomplish the latter, it is desirable to have a septum, which can provide a closure, which is puncturable, and is capable of resealing in a leak-proof manner even after multiple punctures. For example, a reaction vessel such as the cell culture device disclosed in U.S. application number 09/526,006 (the disclosure of which is herein incorporated by reference in its entirety), may further comprise a septum which is inserted and extends into an access port. The septum should permit the

introduction of a tip through the septum and into the access port, seal tightly around the tip to prevent leakage through the septum while the tip is present in the septum, allow withdrawal of the tip without unduly restricting the passage of the tip through the septum, and allow for resealing of the septum in maintaining a barrier to contamination of the contents inside the reaction vessel.

To maintain a barrier to contamination of the contents inside the reaction vessel, three important functions of a septum are: to form a seal around a tip which is inserted into a septum; to reseal after the tip has been withdrawn; and to withstand repeated accessing by a tip in maintaining a leak-proof sealing. A drawback of conventional septum designs can be described as "septum mechanical failure." FIG. 1 illustrates this drawback of conventional septum designs. As illustrated in FIG. 1, there is a tendency of devices to form leaks when a tip is inserted in a septum. In such a pre-slit septum (containing a hole or slit which extends the length of the septum), gaps **10** are formed by slit deformation around the outer surface of tip **5** where the slit does not conform exactly to the outside surface of the tip resulting in a failure of the slit to completely close at its outer-most ends. This failure leads to a partially open slit. A partially open slit results in passages which create an increased risk of contaminants (e.g., microbes) to enter through open portions of the slit, and to be subsequently introduced through the septum into the sterile environment of the device. Further, conventional septum materials, and structural integrity offered by conventional septum designs, simply break down after multiple tip insertions, thereby also affecting the ability of a septum to seal around a tip or reseal after a tip has been removed.

Additionally, microbes (used herein to encompass bacteria, fungus, viruses, and yeast, particularly those microbes which are known to serve as sources of contamination in cell cultures) easily grow in warm and humid places, environmental conditions in which cells are typically cultured. Thus, a surface of a cell culture exposed to humidity and warmth is

conducive to the growth of microbes. If that surface also serves as an access to the culture chamber of a cell culture device (such as the exterior surface of a septum), then that surface serves as a potential source of microbial contamination of cell cultures contained in the cell culture device if microbes on that surface are carried through the access way by an inserted tip. One method to counter the presence and growth of microbes on the surface is to apply a disinfectant to the surface, by wiping the surface prior to each and every tip insertion. However, application of a disinfectant provides only temporary antimicrobial protection of the treated surface, as once the disinfectant wears off, the surface will continue to present a suitable environment conducive to microbial growth.

Thus, there is a need for a pre-slit septum which, when accommodated by an access port, can minimize leakage through its slit during and after being penetrated by a tip in maintaining a leak-proof seal that serves as a barrier to contamination even after repeatedly being accessed by a tip. Additionally, there is a need for a pre-slit septum which has an antimicrobial agent incorporated therein which can migrate to the exterior surface of the septum in providing antimicrobial protection which is also a barrier to contamination.

Summary of the Invention

It is a primary object of the invention to provide a pre-slit septum which, when accommodated in an access port, can minimize leakage through its slit during and after being penetrated by a tip in maintaining a leak-proof seal that serves as a barrier to contamination even after repeated access by a tip.

It is another object of the invention to provide a pre-slit septum of an elastomeric material and design which is expandable to enlarge the slit as a tip is introduced into the slit, and to close around and sealingly engage the inserted tip to prevent leakage between the tip and slit in maintaining a leak-proof seal.

It is another object of the present invention to provide a septum-access port assembly wherein the access port is configured to compress the centrally-disposed portion of the septum, and the septum is dimensioned to be compressed by the access port, resulting in compression of the septum's slit to close around and sealingly engage the outer surface of an inserted tip to prevent leakage between the tip and slit so as to maintain a leak-proof seal.

It is another object of the invention to provide a pre-slit septum which is very well suited for use in an automated system which permits filling, sampling, and draining of a device containing the septum accommodated by an access port.

It is another object of the present invention to provide a septum-access port assembly which is very well suited for use in an automated system which permits filling, sampling, and draining of a device containing the septum-access port assembly.

It is another object of the present invention to provide a septum having incorporated therein a broad spectrum antimicrobial agent that can effectively control microbial growth throughout the intended life of the septum, in providing a barrier to contamination for a cell culture device having the septum, even after repeated access by a tip.

Briefly, the invention provides for an elastomeric, pre-slit septum which is dimensioned to cause centrally directed compression, when inserted in an access port configured to accommodate the septum, such that: (a) when a tip is inserted into and accesses the slit of the septum-access port assembly, the slit closes around and sealingly engages the outer surface of a tip accessing the septum to prevent leakage between the tip and slit so as to maintain a leak-proof seal; and (b) enhances the ability of the septum to reseal itself ("resealability") after withdrawal of the tip from the slit, even after the septum has been repeatedly accessed by tips. Maintaining a leak-proof seal and substantially increasing the resealability of the septum lowers the risk of contamination of contents in a device containing the septum-access port assembly. In a preferred embodiment, the elastomeric pre-slit septum

further comprises an antimicrobially effective amount of a substantially non-toxic (e.g., to cultured mammalian cells) antimicrobial agent which is incorporated into the matrix (including spaces therein) of the septum material in a manner that allows antimicrobial agent to migrate from the matrix to the exterior surface of the septum when the antimicrobial agent on the septum surface becomes depleted.

These and other objects and advantages of the invention will become more apparent from the following detailed description taken in conjunction with the accompanying drawings.

Brief Description of the Drawings

FIG. 1 is a perspective view of a conventional septum having a tip inserted therethrough;

FIG. 2 is a cross sectional view of a septum according to the present invention;

FIG. 3 is a perspective view of a septum according to the present invention;

FIG. 4 is a front view of a septum according to the present invention;

FIG. 5 is a cross sectional view of an embodiment of a septum-access port assembly according to the present invention;

FIG. 6 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 7 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 8 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 9 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 10 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 11 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 12 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 13 is a cross sectional view of another embodiment of the septum according to the present invention;

FIG. 14 is a cross sectional view of another embodiment of the septum according to the present invention; and

FIG. 15 is a cross sectional view of another embodiment of the septum according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "slit" is used herein, for purposes of the specification and claims, to mean an opening which forms a passageway extending through substantially the entire septum body, as will be more apparent from the following descriptions. When the septum is accommodated by an access port, the slit is normally biased closed but may be openable under pressure of a tip in inserting the tip through the slit in allowing the tip to pass through the opening comprising the slit. The opening may comprise a form which includes, but is not limited to, a slot, a hole, a star-shaped incision, an eye-shaped incision, an incision, and a bore.

The term "device" is used herein, for purposes of the specification and claims, to mean a vessel which is used in scientific and/or biomedical applications in which there is a

closed environment (e.g., chamber) formed by the device, and wherein it may be desired to introduce into or withdraw from the closed environment a fluid, while maintaining the sterility of the closed environment (including the sterility of contents that may be contained therein). In a preferred embodiment, the device is a cell culture device. In a more preferred embodiment, the device is a cell culture device disclosed in U.S. application number 09/526,006. Briefly, in this more preferred embodiment, the cell culture device is comprised of a frame to which is contacted and secured taut thereto, in a leak-proof sealing arrangement, two liquid impermeable membranes. At least one of the membranes is gas-permeable. The chamber of the cell culture apparatus, formed by the frame and membranes, is accessed by at least one access port which extends between the outer surface of the frame and the chamber. The at least one access port serves as a means by which substances (e.g., cells in a fluid and/or tissue culture growth medium) can be introduced into, or withdrawn from, the chamber which is maintained as sterile. The at least one access port is sealed by a septum which comprises an elastomeric, gasket material that fills all or a substantial portion of the access port, and which is sufficiently pliable to be self-sealing; e.g., thereby allowing for penetration by a tip, and resealing after tip withdrawal.

The term "contamination" is used herein, for purposes of the specification and claims, to mean the introduction of microbes (e.g., one or more of bacteria, virus, fungi, yeast, and the like) through the septum and into the closed environment which was maintained as sterile until such introduction occurs.

The term "tip" is used herein, for purposes of the specification and claims, to mean a hollow body which may include, but is not limited to, a micropipette tip, a blunt-ended needle, a syringe needle, a blunt cannula, and the like. In a preferred embodiment, the tip comprises a micropipette tip or a blunt-ended needle.

The term "substantially insoluble in water" is used herein, for purposes of the specification and claims, and with respect to an antimicrobial agent, to mean that the antimicrobial agent is either not soluble in water or has low solubility in water (e.g., has a solubility in water at 20°C of less than 0.1gm/liter, and more preferably of less than 0.05 gms/liter).

The term "substantially non-toxic" is used herein, for purposes of the specification and claims, and with respect to an antimicrobial agent, to mean that the antimicrobial agent, as used in the present invention, lacks toxicity with respect to cultured cells (e.g., mammalian cells) or is of such low toxicity that it does not prevent the growth of the cells in a cell culture device if the antimicrobial agent contacts the cells, as will be more apparent from the following descriptions.

An elastomeric septum **21** is illustrated in FIGS. 2-5 and is preferably adapted to be inserted into an access port such as that of a cell culture device and to receive a variety of sizes of tips. Septum **21** comprises septum body **23**, centrally-disposed curved surface **25** on at least one end of septum body **23**, and a centrally located slit **27**. The centrally-disposed curved surface may be of a generally concave, convex, or conical shape. In a preferred embodiment, the centrally-disposed curved surface is concave and present on each end of the septum, as illustrated in FIGS. 2, 3, and 5. Other embodiments of the shape of a septum according to the present invention are illustrated in FIGS. 6 through 15. A preferred shape of the septum may be used to the exclusion of a shape other than the preferred shape. The septum is comprised of a suitable elastomeric material, and may further comprise one or more additives such as a colorant, filler, and the like. The elastomeric material may be natural or synthetic. The elastomeric material may be a material including, but not limited to, silicone rubber, fluoro-carbon rubber, butyl rubber, polychloroprene rubber, a silicone elastomer composite material, thermoplastic elastomer, medical grades of silicone rubber,

polyisoprene, a synthetic isoprene, and a combination thereof. In a preferred embodiment, the elastomeric material is substantially nontoxic to cultured cells (e.g., mammalian cells of a cell culture). Additionally, it is preferred that the elastomeric material is compatible with sterilization processes such as gamma irradiation. In further considering the material comprising the septum body, the elastomeric material may be selected to have a Shore A durometer within the range of from about 30 to about 80. Preferably, the elastomeric material composition and durometer provide a combination that provides superior resealing qualities, particularly when utilized in the septum-access port assembly according to the present invention, as well as certified as nontoxic to cultured cells by a standard assay known in the art. One preferred combination is a septum body comprised of a thermoplastic rubber with a Shore A durometer in the range of from about 45 to about 65, and which has the desired resealing properties when used according to the present invention so that leakage does not occur even after being repeatedly accessed by a tip. In a more preferred combination, the septum body is comprised of a thermoplastic rubber marketed as SANTOPRENE (available from Advanced Elastomer Systems, USA) with a Shore A durometer of about 55. The septum may be manufactured using methods known in the art, such as by a molding process.

The precise dimensions of the septum may be varied depending on factors such as the depth and size of the access port, the forces needed to maintain the septum in position in a radially compressed manner once inserted into and accommodated by the access port, the septum composition (e.g., type of elastomeric material), and the composition of the walls of the access port which contacts the septum body. As illustrative of dimensions of the septum, the length **32** of the septum body from edge to edge is about 3.8 mm, and the width dimension **34** of the septum body is about 5.9 mm. The precise dimensions of the slit may be, in part, determined by the choice of elastomeric material used in construction of the

septum, the septum dimensions, and the different sizes of tips desired to be accommodated by the septum. In continuing with the illustrative dimensions of the septum, the slit length is about 3.0 mm in extending entirely through the length of the septum, and the diameter of the slit is about 0.8 mm. The precise dimensions of the access port, in part, will be determined by the size and composition of the septum, the type of device, and the choice of material used in construction of the access port. Further, in a preferred embodiment wherein the septum is generally cylindrical, it also preferred that the access port (particularly the septum-receiving portion as described in more detail herein) is generally oval in enabling the access port to compress the inserted septum in accordance with the present invention. In continuing with illustrative dimensions, and consistent with an illustrative dimension of the septum as having a radius of 5.9 mm, the septum-receiving portion of the access port may comprise an oval that is 4 mm by 6.8 mm. The septum may then be compressed by between approximately 10% and 35% to be inserted into and friction fitted with the access port.

In a preferred embodiment, the septum further comprises an antimicrobial agent that is incorporated therein in an effective amount to allow the septum to continuously inhibit microbial growth and promote a microbial-free surface during the useful life of the septum. Also provided is an elastomeric septum, dimensioned to be compressed by an access port (e.g., of a device for culturing cells) so as to compress the septum's slit to close around and sealingly engage the outer surface of an inserted tip to prevent leakage between the tip and slit so as to maintain a leak-proof seal, wherein the septum comprises an elastomeric material and an antimicrobial agent mixed and formed into the elastomeric septum, wherein the antimicrobial agent becomes incorporated into the elastomeric septum and forms a surface coating on the elastomeric septum, and wherein the antimicrobial agent exhibits migration through the elastomeric septum as the surface coating of antimicrobial agent is depleted.

An antimicrobial agent preferably has a combination of several or all of the following properties:

(a) is incorporated into the spaces in the elastomer matrix, that are normally present, during septum fabrication;

(b) migrates from the matrix to exposed surfaces of the septum when the antimicrobial agent on the septum surface has been depleted;

(c) has sufficient heat stability so as to retain an effective potency of antimicrobial activity after being exposed to temperatures needed to mold the elastomeric material in fabricating the septum (e.g., withstand temperatures involved in melting the septum material);

(d) is substantially non-toxic with respect to cultured cells, as may be encountered if the antimicrobial agent comes in contact with cells being cultured in a cell culture device;

(e) is dispersible in the elastomeric material used to fabricate the septum;

(f) has broad spectrum antimicrobial activity, particularly against microbes commonly encountered in cell culture environments, and more preferably, against gram-positive bacteria, gram-negative bacteria, viruses, yeast, and fungi; and

(g) is provided in the septum in an effective amount to inhibit microbial growth throughout the useful life of the septum (e.g., for the period that the septum is incorporated as part of a cell culture device, and for the period of use of the cell culture device to culture cells).

The antimicrobial agent may be a single agent or a combination of agents. In a preferred embodiment, the antimicrobial agent is non-ionic and substantially insoluble in water. Suitable non-ionic antimicrobial agents may include, but are not limited to, phenol derivatives, diphenyl derivatives, diphenyl ethers, chlorinated phenoxys, dichlorophenes, and the like. Specific examples may include, but are not limited to, triclosan (2,4,4'-trichloro-2'hydroxydiphenyl ether), 5-chloro-2-(2,4-dichlorophenoxy)phenol, and 2-2'-methylene-bis-

4-chloro-phenol. Other suitable antimicrobial agents may include, but are not limited to, 3-(trifluomethyl)-4,4'-dichloro-carbanilide, or a cationic agent that is substantially insoluble in water. Examples of the latter may include, but are not limited to, biguanide compounds or salts thereof, and more preferably may comprise polyhexamethylene biguanide hydrochloride. The antimicrobial agent may further comprise a stabilizer, which is an effective amount to protect the potency of the antimicrobial agent during the process of fabricating the septum, such as an anti-oxidant. Exemplary stabilizers may include, but are not limited to, hindered phenols, polyphenols, phosphates, thioesters, and the like.

The process of incorporating the antimicrobial agent into the septum material will depend on factors which include, but are not limited to, the nature of the antimicrobial agent, the nature of the elastomeric material comprising the septum, and the method of fabricating the septum. In a preferred embodiment, the antimicrobial agent is embedded in the septum during manufacture such as uniformly mixing the antimicrobial agent with the elastomeric material which is in a fluid state prior to molding, and then the mixture is molded to form the septum. For example, an effective amount of the antimicrobial agent may be in powder form or may be mixed with a portion of the elastomeric material in forming a dispersion, and then is gradually mixed with the elastomeric material until a homogenous mixture is obtained. The septum is then formed in the usual manner (e.g., a molding process). In a preferred embodiment, the antimicrobial agent is added to the elastomeric material in forming a mixture, wherein the antimicrobial agent comprises from about 0.05% to about 5% by weight of the mixture; and more preferably, from about 0.2% to about 2% by weight of the mixture. If the mixture further comprises a stabilizer, the stabilizer comprises about 0.01% to about 1% by weight of the mixture. Thus, antimicrobial agent is combined, in a predetermined amount corresponding to the desired antimicrobial activity, with the elastomeric material in a manner that the antimicrobial agent is incorporated into the spaces of the matrix of the

elastomeric material comprising the septum that are normally present. These reservoirs of antimicrobial agent serve to replenish antimicrobial agent that may be depleted at the septum surfaces. More particularly, the antimicrobial agent may migrate from these spaces and through the septum matrix until surface saturation and equilibrium is reached in providing a surface coating of antimicrobial agent that serves as a barrier to microbial contamination, and in continuously inhibiting microbial growth on the septum surface(s) durable over the useful life of the septum.

As illustrated in FIG. 5, provided is a septum-access port assembly or device **41** adapted to sealingly engage a tip, the septum-access port assembly comprising:

an access port **43** comprising a housing, and a passageway extending entirely through the housing, wherein the passageway comprises a septum-receiving portion **45** that is generally oval, and an inwardly extending portion **47** that is tapered downwardly in direction toward an end of the access port opposite of the septum-receiving portion;

an elastomeric septum comprising septum body **23**, centrally-disposed curved surface **25** on at least one end of septum body **23**, and a centrally located slit **27**; wherein after the septum has been inserted into the access port in forming the septum-access port assembly, the access port compresses the centrally-disposed curved surface of the septum which (a) compresses the slit to be normally biased closed, and (b) allows for the slit to be openable and accessed under pressure of a tip in a process of inserting the tip through the slit and wherein the slit closes around and sealingly engages the outer surface of an inserted tip to prevent leakage between the inserted tip and slit so as to maintain a leak-proof seal. Alternatively, the passageway comprises only the septum-receiving portion, and the elastomeric septum extends entirely through the access port so that surface **25b** of the septum is in direct contact, and in fluid flow communication, with the chamber of the cell culture device (and contents therein, if any). Generally speaking, the septum is held in place inside and by contact with the

access port housing by a friction fit. The friction fit may further comprise a roughened or threaded surface of the access port housing which is contacted with the inserted septum to enhance the friction fit and to further minimize possible movement of the septum in the access port during use. As the septum is inserted into the access port, the access port housing compresses the septum in exerting pressure concentrated towards the center of the septum in enhancing the ability of the centrally located slit to sealingly engage a tip as well as enhancing the resealability of the septum. In a preferred embodiment in which the passageway comprises both a septum-receiving portion and an inwardly extending portion, the access port is tapered downward towards the inner end of the access port (i.e., the end opposite the septum-receiving portion). The taper in the access port helps direct an inserted tip toward the center of the passageway of the access port. Additionally, the taper may serve as a "stop" for the septum in preventing the septum to be pushed substantially farther into the passageway of the access port such as during the process of inserting a tip into the septum-access port assembly. The taper may also create an additional force on the septum, as a tip is being inserted in the septum, which also compresses the slit to sealingly engage and close around the outer surface of the inserted tip. The access port housing may further include one or more small notches **51** in the housing which is placed at the beginning of the taper as a further preventative measure in precluding the septum from moving further into the passageway of the access port such as from a force encountered when inserting a tip into the septum of a septum-access port assembly. In a preferred embodiment, the access port housing is comprised of plastic or a synthetic resin, and more preferably comprised of polyethylene.

In a preferred illustrative embodiment, molded as part of the frame or housing of a cell culture device is the access port, and inserted therein is the septum in forming the septum-access port assembly. Thus, for example, when part of a cell culture device, the outer

curved surface **25a** of the septum is generally flush with the adjacent surface of the frame of the device, and thus would be exposed to the environment outside of the cell culture device; whereas the inner end **46** of the access port would be the part of the passageway of the access port which would be in fluid flow communication with the chamber of the cell culture device (and contents therein, if any). The septum-access port assembly, and particularly the resealable elastomeric septum, may be used in a cell culture device to maintain a leak proof seal which serves as a barrier against contamination of the cell culture contents within the device, while allowing for fluid addition or fluid removal from the device while maintaining the contents as sterile. In use, the exterior surface of the septum is wiped with alcohol or other disinfectant or antimicrobial substance to remove or kill microorganisms from the external environment that may be present on the exterior surface of the septum. In a preferred embodiment, the septum has an antimicrobial agent incorporated therein and which forms a surface coating (as previously described herein in more detail), thereby obviating the need to wipe the exterior surface of the septum with a disinfectant. The slit of the septum-access port assembly is biased close. A sterile tip is directed into the slit in penetrating the slit and forcing the slit open. The slit septum is sufficiently elastomeric so as to permit the inserted tip to be slid easily therethrough while sealingly engaging and closing around the outer surface of the inserted tip. In one embodiment, the inserted tip may be inserted beyond the septum and into the tapered passageway of the access port. The taper guides the tip to align with the passageway that accesses the chamber. In another embodiment in which the passageway comprises a septum-receiving portion and the septum extends to be in direct contact with the chamber, the inserted tip may be positioned either in the septum at a point close to the access to the chamber, or to extend part way into the chamber. In either embodiment, through the inserted tip a fluid may be introduced into or withdrawn when in fluid flow communication with the chamber of the cell culture device. The inserted tip is

then retracted from the septum-access port assembly, and the septum causes the slit to reseal against the passage of microorganisms and the like, thus maintaining a leak-proof sterile seal. There is a sufficient friction force between the access port and the septum to prevent a pull-out of the septum from the access port during the removal of the tip therefrom.

The foregoing description of the specific embodiments of the present invention have been described in detail for purposes of illustration. In view of the descriptions and illustrations, others skilled in the art can, by applying, current knowledge, readily modify and/or adapt the present invention for various applications without departing from the basic concept, and therefore such modifications and/or adaptations are intended to be within the meaning and scope of the appended claims.

What is claimed:

1. A septum adapted to be compressed by an access port of a device, and further adapted to be accessed by a tip, the septum comprising:

a septum body comprised of an elastomeric material and having a centrally-disposed curved surface on at least one end of the septum body;

a centrally located slit which extends entirely through the septum body;

wherein when the septum is compressed in the access port, the slit is biased closed; and

wherein when the septum is compressed, insertion of a tip causes the slit to be opened and accessed by the tip, while the slit sealingly engages and closes around an outer surface of the inserted tip, in providing a leak-proof seal.

2. The septum according to Claim 1, wherein the centrally-disposed curved surface is concave.

3. The septum according to Claim 1, wherein the centrally-disposed curved surface is convex.

4. The septum according to Claim 1, wherein the centrally-disposed curved surface is conical.

5. The septum according to Claim 1, wherein each of the two ends comprises a centrally-disposed curved surface.

6. The septum according to Claim 1, wherein the centrally-disposed curved surface is concave.

7. The septum according to Claim 1, further characterized by the elastomeric material having a Shore A durometer within the range of from about 30 to about 80.

8. The septum according to Claim 1, wherein the elastomeric material comprises a thermoplastic rubber having a Shore A durometer within the range of from about 45 to about 65.

9. The septum according to Claim 1, wherein the elastomeric material is nontoxic to cultured cells.

10. The septum according to Claim 1, further comprising an antimicrobial agent incorporated into the elastomeric material and forms a surface coating of antimicrobial agent, wherein the antimicrobial agent exhibits migration through the elastomeric material as the surface coating of antimicrobial agent is depleted.

11. The septum according to Claim 10, wherein the antimicrobial agent has properties selected from the group consisting of substantially non-toxic with respect to cultured cells, dispersible in the elastomeric material used to fabricate the septum, has antimicrobial activity against microbes commonly encountered in cell culture environments, is provided in the septum in an amount effective to inhibit microbial growth throughout the useful life of the septum, and a combination thereof.

12. The septum according to Claim 10, wherein the antimicrobial agent is selected from the group consisting of triclosan, 5-chloro-2(2,4-dichlorophenoxy)phenol, and polyhexamethylene biguanide hydrochloride.

13. A septum-access port assembly adapted to sealingly engage a tip, the septum-access port assembly comprising:

an access port comprising a housing, and a passageway extending entirely through the housing, wherein the passageway comprises a septum-receiving portion adapted to receive and compress the septum;

an elastomeric septum comprising a septum body, a centrally-disposed curved surface on at least one end of septum body, and a centrally located slit extending entirely through the septum body;

wherein access port compresses the centrally-disposed curved surface of the septum which

(a) causes a friction fit between the septum and the housing of the access port in holding the septum in position in the access port,

(b) compresses the slit to be normally biased closed, and (c) allows for the slit to be openable and accessed under pressure of a tip in a process of inserting the tip through the slit, and wherein the slit closes around and sealingly engages the outer surface of an inserted tip to prevent leakage between the inserted tip and slit so as to maintain a leak-proof seal.

14. The septum-access port assembly according to Claim 13, wherein the passageway further comprises an inwardly extending portion that is tapered downwardly in direction toward an end of the access port opposite of the septum-receiving portion.

15. The septum-access port assembly according to Claim 13, wherein the access port housing comprises a roughened surface which is contact with the septum in forming a friction fit.

16. The septum-access port assembly according to Claim 13, wherein the access port housing comprises a threaded surface which is contact with the septum in forming a friction fit.

17. The septum-access port assembly according to Claim 13, wherein the access port compresses the septum by exerting a pressure concentrated towards the center of the septum.

18. The septum-access port assembly according to Claim 14, wherein the taper of the access port directs a tip inserted through the septum toward the center of the inwardly extending portion of the passageway of the access port.

19. The septum-access port assembly according to Claim 14, wherein the taper contacts the septum and holds the septum in position.

20. The septum-access port assembly according to Claim 13, wherein the access port housing further comprises one or more notches in the housing of the access port, and wherein the one or more notches contacts the septum in holding the septum in position.

21. The septum-access port assembly according to Claim 13, wherein the septum-receiving portion is generally oval, wherein the septum is generally cylindrical before being

compressed by the access port, and wherein the septum becomes generally oval when received and compressed by the access port in forming the septum-access port assembly.

22. The septum-access port assembly according to Claim 13, further characterized as comprising a barrier to contamination.

23. The septum-access port assembly according to Claim 13, wherein the septum is positioned in the access port so as to present a wipeable surface of the septum.

24. The septum-access port assembly according to Claim 13, wherein the septum further comprises an antimicrobial agent incorporated into the elastomeric septum and forms a surface coating of antimicrobial agent, wherein the antimicrobial agent exhibits migration through the elastomeric septum as the surface coating of antimicrobial agent is depleted.

25. The septum-access port assembly according to Claim 24, wherein the antimicrobial agent has properties selected from the group consisting of substantially non-toxic with respect to cultured cells, dispersible in an elastomeric material used to fabricate the elastomeric septum, has antimicrobial activity against microbes commonly encountered in cell culture environments, is provided in an amount effective to inhibit microbial growth throughout the useful life of the septum, and a combination thereof.

26. The septum-access port assembly according to Claim 24, wherein the antimicrobial agent is selected from the group consisting of triclosan, 5-chloro-2(2,4-dichlorophenoxy) phenol, and polyhexamethylene biguanide hydrochloride.

27. A method for providing an elastomeric septum of a cell culture device with antimicrobial activity, the method comprising incorporating an antimicrobial agent into elastomeric material in fabricating the septum.

28. The method according to Claim 27, wherein the antimicrobial agent, incorporated into the elastomeric septum, forms a surface coating of antimicrobial agent, wherein the antimicrobial agent exhibits migration through the elastomeric septum as the surface coating of antimicrobial agent is depleted.

29. The method according to Claim 27, wherein the antimicrobial agent has properties selected from the group consisting of substantially non-toxic with respect to cultured cells, dispersible in an elastomeric material used to fabricate the elastomeric septum, has antimicrobial activity against microbes commonly encountered in cell culture environments, is provided in an amount effective to inhibit microbial growth throughout the useful life of the elastomeric septum, and a combination thereof.

30. The method according to Claim 27, wherein the antimicrobial agent is selected from the group consisting of triclosan, 5-chloro-2(2,4-dichlorophenoxy) phenol, and polyhexamethylene biguanide hydrochloride

31. An elastomeric septum for use with a cell culture device, the elastomeric septum comprising a mixture of an elastomeric material and an antimicrobial agent formed into the elastomeric septum, wherein the antimicrobial agent becomes incorporated into the elastomeric septum and forms a surface coating on the elastomeric septum, and wherein the

antimicrobial agent exhibits migration through the elastomeric septum as the surface coating of antimicrobial agent is depleted.

32. The elastomeric septum according to Claim 31, wherein the antimicrobial agent has properties selected from the group consisting of substantially non-toxic with respect to cultured cells, dispersible in an elastomeric material used to fabricate the elastomeric septum, has antimicrobial activity against microbes commonly encountered in cell culture environments, is provided in an amount effective to inhibit microbial growth throughout the useful life of the elastomeric septum, and a combination thereof.

33. The elastomeric septum according to Claim 31, wherein the antimicrobial agent is selected from the group consisting of triclosan, 5-chloro-2(2,4-dichlorophenoxy) phenol, and polyhexamethylene biguanide hydrochloride.

34. The elastomeric septum according to Claim 31, wherein the septum is adapted to be compressed by an access port of the cell culture device, and further comprises: a septum body comprised of an elastomeric material and having a centrally-disposed curved surface on at least one end of the septum body; a centrally located slit which extends entirely through the septum body; wherein when the septum is compressed in the access port, the slit is biased closed; and wherein when the septum is compressed, insertion of a tip causes the slit to be opened and accessed by the tip, while the slit sealingly engages and closes around an outer surface of the inserted tip, in providing a leak-proof seal.

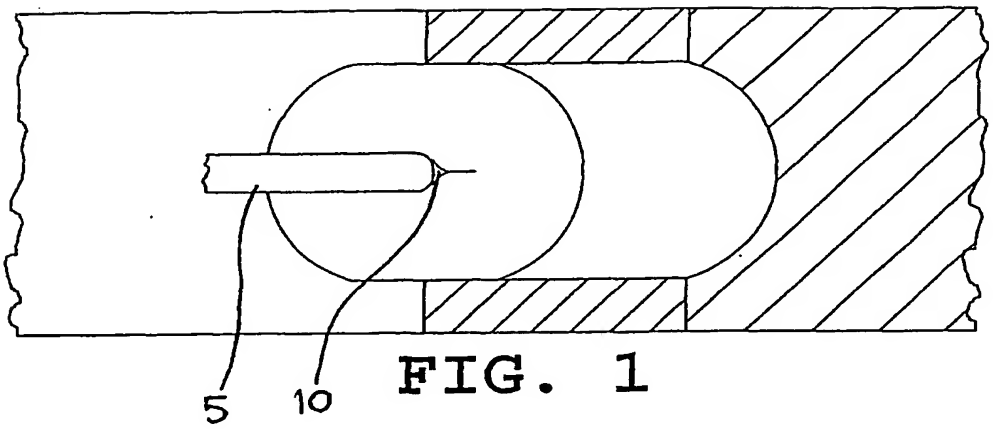

FIG. 1

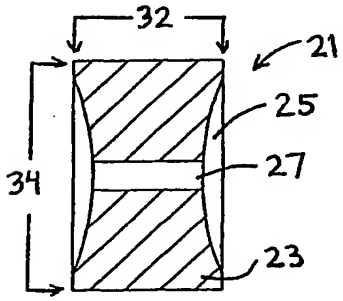

FIG. 2

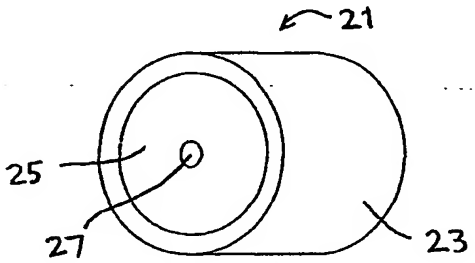

FIG. 3

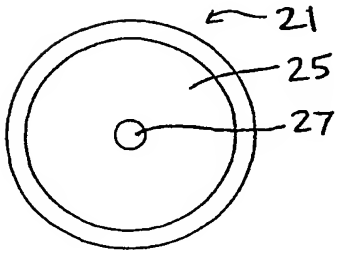

FIG. 4

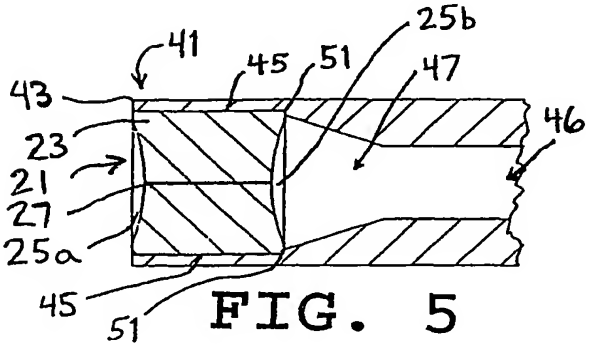

FIG. 5

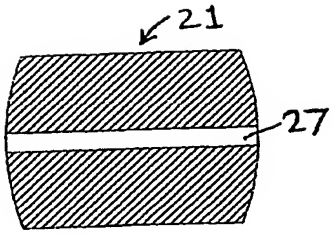

FIG. 6

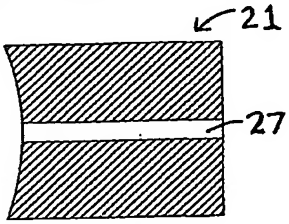

FIG. 7

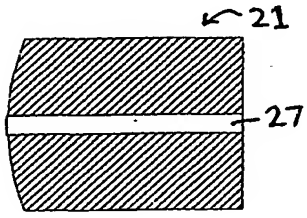

FIG. 8

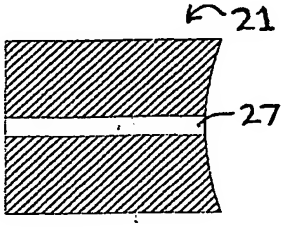

FIG. 9

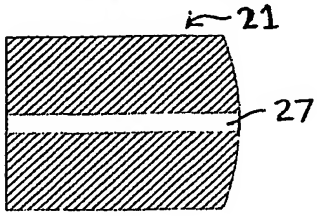

FIG. 10

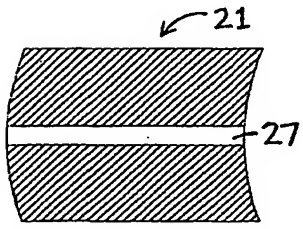

FIG. 11

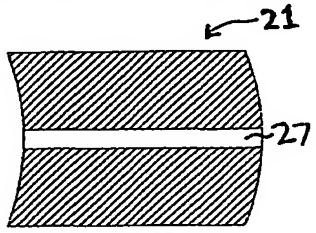

FIG. 12

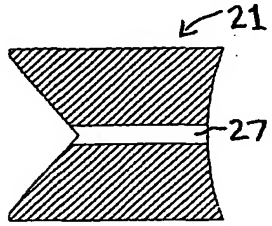

FIG. 13

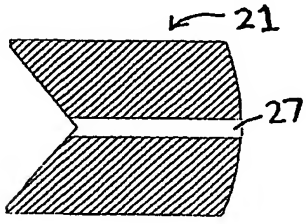

FIG. 14

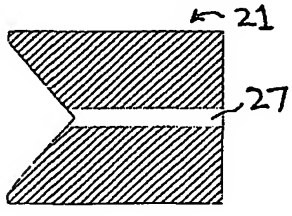

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/43724

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12M 1/24
US CL : 435/304.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/283.1, 288.1, 304.1, 307.1; 215/247; 604/201, 205, 242, 246, 249, 256, 415; 220/Dig. 19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P — Y,P	US 6,171,287 B1 (LYNN et al.) 09 January 2001 (09.01.2001), see entire document.	1, 2, 4, 6-11, 13, 17, 20, 22-25, 27-29, 31, 32, 34 ——— 3, 5, 12, 14-16, 18, 19, 21, 26, 30, 33
Y	US 5,163,902 A (LYNN et al.) 17 November 1992 (17.11.1992), see column 5, lines 29-33.	10-12, 24-34
Y	US 5,354,275 A (BEHNKE et al.) 11 October 1994 (11.10.1994), see column 2, lines 22-27).	21
Y	US 3,853,127 A (SPADEMAN) 10 December 1974 (10.12.1974), see entire document.	21
X — Y	US 5,833,674 A (TRUNBULL et al.) 10 November 1998 (10.11.1998), see entire document.	1, 2, 4-9, 13, 17, 22, 23 ——— 3, 10-12, 14-16, 18-21, 24-34

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search
20 June 2002 (20.06.2002)

Date of mailing of the international search report
16 JUL 2002

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/43724

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2,546,672 A (LE CLAIR) 27 March 1951 (27.03.1951), see element 50.	15, 16
X — Y	US 5,405,331 A (BEHNKE et al.) 11 April 1995 (11.04.1995), see entire document.	1, 2, 5-9, 13, 17, 22, 23 ——— 3, 4, 10-12, 14-16, 18-21, 24-34
Y	US 5,114,400 A (LYNN) 19 May 1992 (19.05.1992), see entire document.	14, 18, 19
Y	US 4,723,950 A (LEE) 09 February 1988 (09.02.1988), see column 4, lines 1-16.	12, 26, 30, 33
X — Y	US 5,785,692 A (ATTERMEIER et al.) 28 July 1998 (28.07.1998), see entire document.	1-4, 6-9, 13, 17, 22, 23 ——— 5, 10-12, 14, 18, 19, 24-34